REMARKS

Claims 19-29 are pending. Claims 26-29 presently stand withdrawn as being drawn to non-elected subject matter. Claims 19-25 are presently under examination. No claim is being amended at this time. The foregoing listing of claims is being provided for the convenience of the Office.

Rejection under 35 U.S.C. § 103

According to the Office Action (page 3): "[c]laims 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aranov et al and Caplus Abstract Acheson and Ana Castro Peripheral and Dual Binding site Acetylcholinesterase Inhibitors."

It is Applicants' understanding that the Office is citing the following references in this rejection:

Alex M. Aronov et al., *Antimicrobial Agents and Chemotherapy* **2001**, *45*, 2571-2576;

R. Morrin Acheson et al., *Journal of Chemical Research Synopses* **1983**, 2-3; and

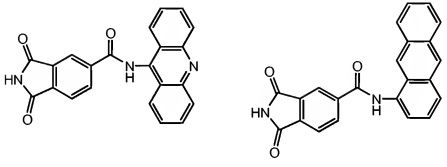
Ana Castro and Ana Martinez, *Mini Reviews in Medicinal Chemistry* **2001**, *1*, 267-272.

The aforementioned references are referred to herein as "Aronov," "Acheson," and "Castro," respectively.

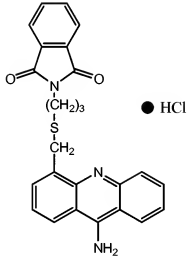
[I] The rejection

[A] *Compounds specifically mentioned in the rejection* (Office Action, pages 5-6)

[1] In Aronov (referred to hereinafter as "the Aronov FIG.1 compounds"):



[2] In Acheson (referred to hereinafter as "the Acheson compound"):



[3] The Office refers to "fig 2" in Castro, which occurs at page 269 of said reference. This figure includes nine structural formulae. In one of these formulae, the substituent corresponding to Applicants' variable X is isoindoline-1,3-dione ring; however, it is connected to a complex tetracyclic ring that is quite dissimilar to the left-hand tricyclic ring that is required by the present claims. Two of the formulae in Figure 2 of Castro include one or two 1,2,3,4-

tetrahydroacridine rings. The remaining formulae in Figure 2 effectively bear no resemblance to the claimed compounds.

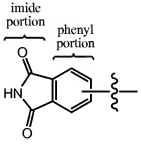
[B] The Office, referring to the Aronov compounds (*supra*), states "[t]he difference is the point of attachment to the indole ring" (Office Action, page 5). The Office, referring to the Acheson compound (*supra*), states "[t]he difference again is the position of attachment" (Office Action, page 5). The Office then goes on to state (Office Action, pages 5-6):

> The Aronov reference attachment of the indole group on the same tricyclic core. And Acheson teaches the attachment but at a different position on the tacrine. These compounds are very similar in structure and activity to the applicants compounds. The teaching of the indole dione core attaches in different ways to the acridine is clearly taught. Even various linkers are taught. Castro discloses the dual binding ACHE inhibitors. In fig 2 page 260. It teaches the tacrine and the indolyl dione group. Attached via the N. Thus clearly teaching that attaching via the N of the phtaladimide would retain its properties. ...
>
> As the attachment of the dione at N position is taught according to Acheson and Castro also teaches the phathalidimide attached via the N to have AChE inhibitor activity., one of skill in the art would be motivated to modify the compounds of Aranov by changing the point of attachment.

[II] The references cited by the Office

[A] *Aronov*

Aronov discloses compounds, e.g., the Aronov FIG.1 compounds delineated above, which are "based on a phthalimide scaffold" (see, Aronov at page 2572). These compounds all contain the phthalimide group shown below as part of their chemical structure and are referred to (collectively) hereinafter as the "Aronov phthalimide compounds":



As indicated above, the imide portion of the phthalimide group is unsubsituted (i.e., has the formula -C(O)-N**H**-C(O)-) in all of the Aronov phthalimide compounds, whilst the phenyl portion is substituted with a secondary amide.

As explained in the passage from Aronov below, Aronov specifically selected the phthalimide scaffold as a starting point for screening, and a fair reading of Aronov would lead one to reasonably conclude that the imide portion of the phthalimide group represents the "business end" of the Aronov phthalimide compounds (Aronov at page 2572, bold emphasis in original; underline emphasis added):

> **Choice of scaffold and chemistry.** Having previously reported on the successful design of selective submicromolar *T. foetus* HGXPRT inhibitors based on the phthalimide scaffold, we looked into the possibility of designing inhibitors that would target a related enzyme *G. lamblia* GPRT. Due to the specificity difference between the *T. foetus* and *G. lamblia* PRTs, phthalimide would not be generally expected to serve as an efficient scaffold in the context of the GPRT binding site. The imide portion of the molecule mimics the C_6-N_1-C_2 of xanthine, one of the natural substrates of HGXPRT. It could be expected to form unfavorable interactions with the backbone carbonyls of Asp 181 and Asp187, which directly interact with the exocyclic N2 of guanine. However, due to the general similarity in the shape of the active sites between the *T. foetus* and *G. lamblia* PRTs, we decided that screening of our in house phthalimidocarboxanilide database for inhibitory activity against GPRT could

potentially result in identification of a starting point for our lead discovery efforts. This approach resulted in identification of two active molecules (Fig.1). Both phthalimide derivatives contained bulky fused ring systems that most likely derived much of their binding energy from burying the large hydrophobic substituents. We set out to design smaller, less lipophilic molecules that would retain their activity against GPRT.

For purposes of clarification, the phthalimide group in the Aronov phthalimide compounds corresponds to variable "X" in Applicants' formula (I). The definition of variable "X" in claim 1 excludes phthalimide groups oriented in the manner found in the Aronov phthalimide compounds.

Finally, the only SAR described in Aronov concerns modifications to the substituent on the secondary amide, which is attached to the phenyl portion of the phthalimide group. More specifically, these modifications involved replacing the tricylic structures found in the Aronov FIG.1 compounds with "smaller" substituents (see, e.g., last sentence in the above-quoted passage from Aronov). Indeed, a library of compounds so dimensioned are prepared and tested in Aronov. Again, for purposes of clarification, the secondary amide substituent in the Aronov phthalimide compounds corresponds to the left hand ring structure in Applicants' formula (I), which must be a tricyclic ring. Thus, the SAR modifications to the Aronov FIG.1 compounds discussed above would have led the skilled artisan even further away from the compounds presently claimed.

[B] *Acheson*

The Office specifically relies upon "Caplus English abstract Acheson" to characterize Acheson. Contrary to the assertions of the Office, this abstract, while providing the chemical structure of the Acheson compound (*supra*), says nothing about whether the Acheson compound has any biological activity. The short paper cited in the aforementioned abstract does not even show (or even refer to) the chemical structure of the Acheson compound, much less say whether said compound is active. Applicants have enclosed what is believed to be the full article that discloses the chemical structure of the Acheson compound. The article has the same title and authors as those listed on the abstract, but appears to have published in "J Chem Research (M)"

instead of "J Chem Research (S).[1]" We refer to this article hereinafter as "the Acheson article." The Acheson compound appears on page or frame 0110 of the Acheson article. The vast majority of the compounds shown in the Acheson article have structures that are different from the Acheson compound. Further, the focus of the Acheson article is on how the compounds shown therein were synthesized and not on whether the compounds have any biological activity. No biological data are provided for any of the compounds shown in the Acheson article, including the Acheson compound.

Finally, it is apparent from the chemical structure of the Acheson compound that several modifications of the Acheson compound would needed in order to arrive at those presently claimed.

[C] *Castro*

Castro is a review of compounds that purportedly inhibit acetylcholinesterase. The Office refers to "fig 2" in Castro, which occurs at page 269 of said reference. This figure includes nine structural formulae. In one of these formulae, the substituent corresponding to Applicants' variable X is isoindoline-1,3-dione ring; however, it is connected to a complex tetracyclic ring that is quite dissimilar to the left-hand tricyclic ring that is required by the present claims ("compound **3**" in "fig 2" in Castro). According to the Office, Castro " teaches the tacrine and the indoyl dione group. Attached via the N. Thus clearly teaching that attaching via the N of the phtaladimide would retain its properties" (Office Action, page 6). This conclusion appears to be somewhat of an over-generalization of Castro. In particular, the complex tetracyclic ring in compound **3** of Castro has essentially the same ring structure as that of Galanthamine, a compound already known as of Applicants' filing date to be used for the treatment of Alzheimer's disease. See, Mary et al., *Bioorganic & Medicinal Chemistry* **1998**, 6, 1835-1850.

[1] It is believed that the descriptors (M) and (S) stand for. "Miniprint Microfiche Edition" and "Synopses," respectively.

[III] The Federal Circuit in *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.* 533 F.3d 1353, 1358 (2008) discussed the requirements for establishing whether a claimed compound is *prima facie* obvious over a reference compound (emphasis added):

> The Supreme Court's analysis in *KSR* thus relies on several assumptions about the prior art landscape. First, *KSR* assumes a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions. Second, *KSR* presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound. *See Takeda*, 492 F.3d at 1357 ("**Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound**."). Third, the Supreme Court's analysis in KSR presumes that the record before the time of invention would supply some reasons for narrowing the prior art universe to a "finite number of identified, predictable solutions," 127 S.Ct. at 1742. In *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 (Fed.Cir.2008), this court further explained that this "easily traversed, small and finite number of alternatives ... might support an inference of obviousness." To the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.
>
> **In other words, post- *KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound**.

[IV] According to MPEP § 2143.01 (bold emphasis in original):

> **VI. THE PROPOSED MODIFICATION CANNOT CHANGE THE PRINCIPLE OF OPERATION OF A REFERENCE**
>
> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary

reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.).

[V] According to the Office Action (page 6, emphasis added):

> As the attachment of the dione at N position is taught according to Acheson and Castro also teaches the phthalidimide attached via the N to have AChE inhibitor activity., one of skill in the art would be motivated to modify the compounds of Aranov by changing the point of attachment.

Applicants respectfully disagree and respectfully submit that one of ordinary skill in the art would not have been led to modify the Aronov FIG.1 compounds (or any other compound in Aronov for that matter) in the manner proposed by the Office because doing so would change the principle of operation of the Aronov FIG.1 compounds. This is discussed in more detail below.

[A] Aronov deliberately chooses compounds which are "based on a phthalimide scaffold" for screening. These compounds not only **all** contain a phthalimide group, but contain a phthalimide group in which the imide portion is unsubstituted and available for interaction with residues in the active site of the target. Moreover, a fair reading of Aronov leads one to reasonably conclude that the unsubstituted imide portion of the phthalimide group represents the "business end" (at least for binding) of the Aronov phthalimide compounds:

> Due to the specificity difference between the *T. foetus* and *G. lamblia* PRTs, phthalimide would not be generally expected to serve as an efficient scaffold in the context of the GPRT binding site. The imide portion of the molecule mimics the C_6-N_1-C_2 of xanthine, one of the natural substrates of HGXPRT. It could be expected to form unfavorable interactions with the backbone carbonyls of Asp 181 and Asp187, which directly interact with the exocyclic N2 of guanine. However, due to the general similarity in the shape of the active sites between the *T. foetus* and *G. lamblia* PRTs, we decided that screening of our in house phthalimidocarboxanilide database for inhibitory activity against GPRT could potentially result in identification of a starting point for our lead discovery efforts. This approach resulted in identification of two active molecules (Fig.1)

[B] According to MPEP § 2143.01:

> If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.

As discussed above, the (unsubstituted) imide portion of the phthalimide group in the Aronov FIG.1 compounds certainly appears to represent the "business end" (at least for binding) of these compounds. One of ordinary skill in the art would therefore reasonably conclude that the imide portion of the phthalimide group is connected in at least some way to the principle of operation of the Aronov FIG.1 compounds. Modifying the Aronov FIG.1 compounds in the manner proposed by the Office -- i.e., "changing the point of attachment" (Office Action, page 6) of the phthalimide group from the phenyl portion to the imide portion (*via* the imide nitrogen)-- would, however, remove all signs of this unsubstituted and interactive imide moiety (-C(O)-N**H**-C(O)-) from the Aronov FIG.1 compounds. In short, one would no longer have a compound based on Aronov's phthalimide scaffold. Accordingly, one of ordinary skill in the art would recognize that modifying the Aronov FIG.1 compounds in the manner proposed by the Office would change the principle of operation of the Aronov FIG.1 compounds because the interactive imide moiety would no longer be present in the Aronov FIG.1 compounds. Further, nothing in Acheson and Castro (either alone or in combination) would lead one to conclude otherwise. In conclusion, one of ordinary skill in the art would not have been led by Aronov, Acheson, and Castro (either alone or in combination) to modify the Aronov FIG.1 compounds (or any other compound in Aronov for that matter) in the manner proposed by the Office because doing so would change the principle of operation of the Aronov FIG.1 compounds.

In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Double Patenting

Claims 19-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 16-24 of USSN 10/887,974. The present claims and the claims pending in USSN 10/887,974 (copy enclosed) do not overlap, and Applicants respectfully request that the rejection be reconsidered and withdrawn for at least this reason.

Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 18043-0003US1 / PC785841US.

Respectfully submitted,

Date: August 23, 2010

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